REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative, as noted below.

Status of the Claims

Pending claims

Claims 1 to 25 are pending. Claims 12 to 24 have been withdrawn from consideration. Thus, claims 1 to 11 and 25, are pending and under consideration.

Claims canceled and added in the instant amendment

In the present response, claims 2, and 12 to 24 are canceled, without prejudice or disclaimer, and claims 26 to 36, are added. Accordingly, after entry of the instant amendment, claims 1, 2 to 11, and 25 to 36, will be pending and under examination.

Outstanding Rejections

The rejection of claims 1 to 11, is maintained, and claim 25 is newly rejected, under 35 U.S.C. §103(a) as allegedly obvious over Morton, et al., WO 95/15338; hereinafter "Morton") in view of The Interferon Beta Multiple Sclerosis Study Group (Neurology, 1993, 43:655-661; hereinafter "the MS Study"). Claims 1, 2 and 3 to 7, are newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement. Claims 1 to 7, are newly rejected under 35 U.S.C. § 112, second paragraph.

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the amended claims. For example, support for claims directed to methods comprising combined cpn10 and IFN-β treatment to achieve a "markedly improved ability" to treat MS or delay relapse following

cessation of other treatments can be found, inter alia, on page 12, lines 5 to 6, of WO 00/43033 (the publication of this application, which is a §371 national phase of PCT/AU00/00032). Support for claims directed to methods wherein the IFN-β is administered at a dose below that which produces clinically significant IFN-β-induced side effects in the individual can be found, inter alia, on page 12, lines 10 to 13. Support for claims directed to methods of treating multiple sclerosis (MS) in an individual taken off IFN-β treatment or having reduced dose IFN-β treatment because of clinically significant IFN-β-induced side effects can be found, inter alia, on page 12, lines 23 to 29. Support for claims directed to methods of treating multiple sclerosis (MS) wherein the pharmaceutically effective amount of IFN-β comprises the equivalent of administering about 1 to 10, or 4 to 6, Million International Units (MIU) of IFN-β, can be found, inter alia, on page 13, lines 7 to 25. Support for claims directed to methods of treating multiple sclerosis (MS) wherein the pharmaceutically effective amount of cpn10 comprises the equivalent of administering about 5 to 60, or 10 to 30, mg of cpn10 to a 70 kg individual, can be found, inter alia, on page 13, lines 7 to 25.

Accordingly, no new matter has been added and the amendment can be properly entered.

Rejection under 35 U.S.C. §103

The rejection of claims 1 to 11, is maintained, and claim 25 is newly rejected, under 35 U.S.C. §103(a) as allegedly obvious over Morton in view of the MS Study.

Applicants have responded to this rejection regarding claims 1 to 11, in previous responses, and expressly incorporate those remarks herein, and also apply these arguments to the newly rejected claim 25.

However, while reiterating and expanding on their prior traversal, Applicants will provide sufficient new argument, including evidence that the art taught away from the instant invention, and evidence of secondary indicia of nonobviousness, including unexpected results and long felt need, such that the rejection under section 103 can be properly withdrawn.

The cited Morton describes the use of chaperonin 10 (cpn10) for the treatment of experimental allergic encephalomyelitis (EAE), an art-accepted animal model for the human

multiple sclerosis (MS). Morton does not teach or suggest administration of IFN-β. The MS Study describes use of IFN-β for the treatment of MS, but does not teach or suggest use of cpn10. Thus, neither reference teaches or suggests the combination of cpn10 and IFN-β for the treatment of MS. Neither Morton nor the MS Study, nor the combination thereof, teaches or suggests that combined cpn10 and IFN-β treatment display a "markedly improved ability" to treat MS or delay relapse following cessation of other treatments (see, inter alia, page 12, lines 5 to 6, of WO 00/43033). Regarding new claim 31, neither Morton nor the MS Study teaches or suggests administering IFN-β at a dose below that which produces clinically significant IFN-β-induced side effects in the treated individual.

Applicants respectfully aver, and provide an expert declaration in support, that not only was there no express or inherent motivation in the cited or prior art to combine these two references, i.e., to use cpn10 and IFN-β in a combined therapeutic regime, but the prior art actually taught away from using cpn10 and IFN-β together in a combination therapy.

As noted in their earlier response, and explained by Dr. Barbara Johnson in the attached Rule 132 expert declaration, the claimed invention is based, inter alia, on the discovery that because cpn10 and IFN-β act via different biological mechanisms they act co-operatively to reduce MS symptoms and decrease relapse frequency. However, as declared by Dr. Johnson, at the time of this invention the art clearly described cpn10 and IFN-β as acting via similar mechanisms. Thus, as declared by Dr. Johnson, at the time of this invention a skilled artisan would not have been able to predict an improved therapeutic effect upon the combined administration of cpn10 and IFN-β, particularly when using a dosage of IFN-β that will not cause clinically significant IFN-β-induced side effects in the patient. In fact, as noted by Dr. Johnson, the art implicitly taught away from the present invention by teaching that cpn10 and IFN-β have the same biological mechanism of action. Thus, the skilled artisan would not have been able to predict an improved therapeutic effect upon the combined administration of cpn10 and IFN-β, or a delay in MS relapse from the combination of cpn10 and IFN-β. Accordingly, Applicants respectfully submit that, inter alia, because the prior art implicitly taught away from the present invention and there was no motivation to combine Morton

or the MS Study, the cited references do not teach or suggest the claimed invention. See paragraphs 6 to 13, pages 2 to 5, of the expert declaration.

It appears the Office remains concerned that the combination of cpn10 and IFN-β is additive, rather than synergistic; see page 3, lines 12 to 14, of the OA. The Office alleges that Table 4 "does not appear" to directly compare the combined treatment to each alone, and, that the data from administration of cpn10 and IFN-β alone "do not appear to be significantly different" from the data for combined cpn10 and IFN-β treatment (page 3, lines 14 to 17, of the OA).

However, Applicants respectfully aver that the data presented in the specification, including Figures 8 and 9, and Table 4, as described the discussion of Example 6 (pages 26 to 28, of WO 00/43033) clearly demonstrate a statistically significant difference between administering cpn10 and IFN-β alone versus combined cpn10 and IFN-β treatment. For example, Figures 8A and 8B show the mean disability score per mouse as a function of days after inoculation of either control, cpn10 alone or combined cpn10 and IFN-β treatment. As summarized in the specification (page 27, lines 15 to 26, of WO 00/43033), if administered together, the combination of recombinant cpn10 (rcpn10) and IFN-β treatment gave greater suppression of disease, as measured through a disability score; albeit the suppressive effect on disability was more apparent during the period of relapse than in primary attack. Figure 9 effectively illustrates a summary of data which clearly shows that combined cpn10 and IFN-β treatment is more effective than cpn10 alone or IFN-β alone; again noting that the suppressive effect on disability was more apparent during the period of relapse than in primary attack. These data are also summarized in table form in Table 4 (page 37 of WO 00/43033).

Dr. Johnson also declares that it is clear from the results provided in the specification that the administration of cpn10 and IFN-β in combination do provide beneficial and synergistic effect over the administration of each alone. Dr. Johnson further declares that the invention achieves this beneficial and synergistic result by using doses of each agent lower than would have been (at the time of the invention) regarded as the optimal dose for each agent used alone. In support, Dr. Johnson notes that in Morton the dose of cpn10 is administered to EAE rats at 15 μg.

Thus, the 2.5 μg administered in one aspect of the methods of the invention can be considered a suboptimal dose. Dr. Johnson also declares that the reference Yu, et al. (1996) J. Neuroimmunol. 64:91-100 (copy attached) similarly teaches an optimal dose of IFN-β higher than that used in one aspect of the methods of the invention; Yu teaches a dose-response curve of IFN-β between 5,000 and 10,000 IU in the treatment of EAE induced by PLP (the same system employed by Morton). See paragraph 13, page 4, of her expert declaration. See paragraphs 6 to 13, pages 2 to 5, of the expert declaration.

A *prima facie* case of obviousness is established only when the teaching from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. The art must suggest how to apply their teachings to the specifically claimed invention.

However, because there was no express or inherent motivation in the cited or prior art to combine the cited references, i.e., to use cpn10 and IFN-β in a combined therapeutic regime, and, as explained by Dr. Johnson, the prior art actually taught away from using cpn10 and IFN-β together in a combination therapy, the rejection under section 103 can be properly withdrawn. Applicants respectfully submit that a *prima facie* case of obviousness has not established by this combination of cited art, and the rejection under 35 U.S.C. §103(a) can be properly withdrawn.

Evidence of secondary indicia of nonobviousness rebuts a possible prima facie case

Applicants submit herein sufficient evidence of secondary indicia of nonobviousness to rebut any possible *prima facie* case. Applicants respectfully aver that their submission of evidence of secondary indicia of nonobviousness overcomes any possible obviousness rejection, even if, *arguendo*, the Patent Office showed sufficient evidence of *prima facie* obviousness.

> The secondary considerations are also essential components of the obviousness determination. See In re Emert, 124 F.3d 1458, 1462, 44 USPQ2d 1149, 1153 (Fed. Cir. 1997) ("Without Emert providing rebuttal evidence, this *prima facie* case of obviousness must stand."). This objective evidence of nonobviousness includes copying, long felt but unsolved need, failure of others, see Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966), commercial success, see In re Huang, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689-90 (Fed. Cir. 1996), unexpected results created by the claimed

> invention, unexpected properties of the claimed invention, see In re Mayne, 104 F.3d 1339, 1342, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997); In re Woodruff, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990), licenses showing industry respect for the invention, see Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997); Pentec, Inc. v. Graphic Controls Corp., 776 F.2d 309, 316, 227 USPQ 766, 771 (Fed. Cir. 1985), and skepticism of skilled artisans before the invention, see In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

In re Rouffet, 47 U.S.P.Q.2D (BNA) at 1456.

Dr. Johnson declares that there was a long-felt need for an invention such as that claimed in this application. She notes that throughout the 20th century scientists and physicians have sought effective treatments for MS with limited success (see Dr. Johnson's expert declaration, paragraph 4, page 1). Dr. Johnson declares that this invention offers a solution to this long felt need by providing an effective therapy using cpn10 and IFN-β together. Dr. Johnson also declares that it is worthy to note that in spite of years of intensive research by many investigators no one had, before the present invention, taught or suggested a therapy for MS comprising combined administration of beta-interferon and chaperonin 10 (see Dr. Johnson's expert declaration, paragraph 5, page 2).

In view of the above remarks and the evidence of secondary indicia of nonobviousness as set forth in the declaration of Dr. Johnson, Applicants submit that they have rebutted any possible *prima facie* case of nonobviousness. Accordingly, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. §103(a).

Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 2 and 3 to 7, are newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement.

Claims 1 and 3 to 7, are newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement, for allegedly not providing reasonable enablement for treatment using suboptimal levels of IFN-β, as set forth in paragraph 3, page 4, of the OA. Although Applicants respectfully traverse, submitting that one skilled in the art, i.e., a clinician treating MS, would have

understood what a clinically suboptimal level of IFN-β would have been, merely to expedite prosecution of the application have amended the claims to address this issue.

Claim 2 is newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement, as set forth in paragraph 4, pages 4 to 5, of the OA. The Office has issues regarding use of the term "prevention." The instant amendment addresses this issue.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1 to 7, are newly rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, as set forth in paragraph 6, page 5, of the OA.

The Office has issues regarding use of the term "suboptimal." The instant amendment addresses this issue.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs, and 35 U.S.C. §103(a). In view of the above, claims in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 524372000100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 7205133.

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Respectfully submitted,

By _____

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